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Cardiovascular Phenotype in HFpEF Patients With or Without Diabetes

A RELAX Trial Ancillary Study

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ABSTRACT

BACKGROUND The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) study was a multicenter, randomized trial of sildenafil versus placebo in heart failure with preserved ejection fraction (HFpEF) with rigorous entry criteria and extensive phenotypic characterization of participants.

OBJECTIVES The aim of this study was to characterize clinical features, exercise capacity, and outcomes in patients with HFpEF with or without diabetes and gain insight into contributing pathophysiological mechanisms.

METHODS The RELAX study enrolled 216 stable outpatients with heart failure, an ejection fraction ≥50%, increased natriuretic peptide or intracardiac pressures, and reduced exercise capacity. Prospectively collected data included echocardiography, cardiac magnetic resonance, a comprehensive biomarker panel, exercise testing, and clinical events over 6 months.

RESULTS Compared with nondiabetic patients (n = 123), diabetic HFpEF patients (n = 93) were younger, more obese, and more often male and had a higher prevalence of hypertension, renal dysfunction, pulmonary disease, and vascular disease ($p < 0.05$ for all). Uric acid, C-reactive protein, galectin-3, carboxy-terminal telopeptide of collagen type I, and endothelin-1 levels were higher in diabetic patients ($p < 0.05$ for all). Diabetic patients had more ventricular hypertrophy, but systolic and diastolic ventricular function parameters were similar in diabetic and nondiabetic patients except for a trend toward higher filling pressures (E/e′) in diabetic patients. Diabetic patients had worse maximal (peak oxygen uptake) and submaximal (6-min walk distance) exercise capacity ($p < 0.01$ for both). Diabetic patients were more likely to have been hospitalized for heart failure in the year before study entry (47% vs. 28%, $p = 0.004$) and had a higher incidence of cardiac or renal hospitalization at 6 months after enrollment (23.7% vs. 4.9%, $p < 0.001$).

CONCLUSIONS HFpEF patients with diabetes are at increased risk of hospitalization and have reduced exercise capacity. Multimorbidity, impaired chronotropic reserve, left ventricular hypertrophy, and activation of inflammatory, pro-oxidative, vasoconstrictor, and profibrotic pathways may contribute to adverse outcomes in HFpEF patients with diabetes. (Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure [The RELAX Study]; NCT00763867) (J Am Coll Cardiol 2014;64:541–9) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

CITP = carboxy-terminal telopeptide of collagen type I

CMR = cardiac magnetic resonance

CSA = cross-sectional area

EF = ejection fraction

HFN = Heart Failure Network

HFpEF = heart failure with preserved ejection fraction

HR = heart rate

hs-cTnI = high-sensitivity cardiac troponin I

LV = left ventricular

mFS = midwall fractional shortening

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

Vo_2 = oxygen uptake

Diabetes adversely affects outcomes of all types of cardiovascular diseases (1). In particular, diabetes is associated with a 70% to 80% increase in mortality and hospitalizations in patients with heart failure with preserved ejection fraction (HFpEF) (2–4), but the underlying mechanisms of this relationship are unclear. Few studies provide detailed phenotypic comparison of diabetic and nondiabetic patients with HFpEF. Notably, although improving exercise capacity is an important treatment goal and common endpoint in clinical trials in HFpEF, the impact of diabetes on exercise capacity and the pathophysiological mechanisms driving such differences have not been evaluated in patients with HFpEF (5,6). Because 30% to 40% of patients with HFpEF have diabetes (2,5,7), understanding whether diabetic HFpEF patients have distinctive characteristics and outcomes may have important implications for clinical management and identification of effective medical therapies for this large patient subgroup.

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The RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) study enrolled both diabetic and nondiabetic patients with HFpEF (5). This rigorously characterized HFpEF cohort, including detailed measurements of exercise capacity, provides the opportunity to evaluate the diabetic HFpEF phenotype. We hypothesized that HFpEF patients with diabetes represent a subgroup with more severe disease with a more severe reduction in exercise capacity, in association with evidence of distinctive pathophysiological mechanisms.

METHODS

PATIENT POPULATION. The rationale, design, inclusion and exclusion criteria, and primary results of RELAX have been reported (5,8). RELAX was a multicenter, randomized 24-week trial of sildenafil versus placebo in 216 stable outpatients with heart failure. Patients were eligible for enrollment if they had an ejection fraction (EF) ≥50%, New York Heart Association (NYHA) functional class II to IV symptoms, stable medical therapy, and objective evidence of heart failure. Patients also had to meet 2 screening criteria: peak oxygen uptake (Vo_2) ≤60% of age- and sex-adjusted normal value (with a respiratory exchange ratio ≥1.0) (9) and either elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥400 pg/ml or B-type natriuretic peptide ≥200 pg/ml) or elevated pulmonary capillary wedge pressure (rest >20 mm Hg or exertional >25 mm Hg). The enrolling sites determined the diagnosis of diabetes and other clinical characteristics. The institutional review board at each enrolling site approved the study protocol, and all patients provided written informed consent.

STUDY PROCEDURES. Baseline testing included a history and physical examination, phlebotomy for biomarkers, Minnesota Living with Heart Failure Questionnaire, measurement of 6-min walk distance, echocardiogram, cardiac magnetic resonance (CMR) (for those in sinus rhythm), and cardiopulmonary exercise testing.

BIOMARKER ASSESSMENT. Assays were performed at the Heart Failure Network (HFN) biomarker core laboratory (University of Vermont, Burlington, Vermont) and included measures of renal function (creatinine and cystatin-C), markers of neurohumoral activation (NT-proBNP, endothelin-1, and aldosterone), fibrosis-related markers (amino-terminal propeptide of procollagen type III, galectin-3, and carboxy-terminal telopeptide of collagen type I [CITP]), and markers of myocardial necrosis (high-sensitivity cardiac troponin I [hs-cTnI]), oxidative stress (uric acid), and inflammation (C-reactive protein).

DOPPLER ECHOCARDIOGRAPHY. Brachial blood pressure and heart rate (HR) were measured while the echocardiogram was being recorded. Left ventricular (LV) cavity dimension and wall thicknesses were measured from 2-dimensional images. LV mass was calculated using the formula recommended by the American Society of Echocardiography and indexed to height$^{1.7}$ (10,11). Reported EF preferentially used biplane Simpson's method, modified Quinones formula, or single-plane volumetric or visual estimate (10). Midwall fractional shortening (mFS) and end-systolic wall stress (circumferential end-systolic stress) were measured as previously described (12). Contractility (stress corrected-mFS) was assessed by indexing mFS to (log-transformed) circumferential end-systolic stress. Stroke volume was calculated from the time velocity integral of the pulsed wave Doppler signal of LV outflow tract flow and area. Pulmonary artery systolic pressure was calculated from the peak tricuspid regurgitant velocity and the estimated right atrial pressure using the simplified Bernoulli equation. Early diastolic medial and lateral mitral annular tissue velocity (e′), early mitral inflow deceleration time, and the ratio of the early transmitral flow velocity (E) to e′ (E/e′) were used to estimate

LV relaxation, LV stiffness, and LV filling pressure, respectively. Pulse pressure and mean arterial pressure were calculated using standard formulas. End-systolic pressure was estimated as 0.9 • systolic blood pressure (13). Effective arterial elastance (end-systolic pressure/stroke volume), systemic arterial compliance (stroke volume/pulse pressure) and systemic vascular resistance (mean arterial pressure/cardiac output • 80) were derived as previously described (13). The HFN core echocardiography laboratory (Mayo Clinic, Rochester, Minnesota) completed all measurements according to the American Society of Echocardiography recommendations (10,14).

CARDIAC MAGNETIC RESONANCE. Brachial blood pressure and HR were measured during CMR. Aortic distensibility was measured using aortic maximal cross-sectional area (CSA_{max}) and minimal CSA (CSA_{min}) as (aortic CSA_{max} − aortic CSA_{min})/(aortic CSA_{min} × pulse pressure) (15). Calculation of volumes and mass was performed according to Simpson's rule on traced endocardial and epicardial short-axis LV images by the HFN core CMR laboratory (Duke University, Durham, North Carolina).

CARDIOPULMONARY EXERCISE TESTING. A detailed description of the RELAX cardiopulmonary exercise testing protocol, methodologies, and calculations has been published (5,8). All measurements were performed by the HFN core cardiopulmonary exercise testing laboratory (Harvard University, Cambridge, Massachusetts).

STATISTICAL ANALYSIS. Data are reported as median (25th, 75th percentiles) or frequency (%) as appropriate. Between-group comparisons used Wilcoxon rank and chi-square tests. Linear regression models were used to evaluate the relationship between diabetes and peak Vo_2 or 6-min walk distance, adjusting for factors known to influence exercise capacity in other studies and in the RELAX study (exercise modality, age, sex, body size, chronotropic response, and hemoglobin) (16). Chronotropic incompetence was determined as described previously and chronotropic index = (peak HR − resting HR)/[(220 − age) − resting HR] (17). The association between diabetes and hospitalization (≥1 hospitalizations) for cardiovascular or renal causes during the 6-month study period was assessed by a chi-square test and a multivariable Cox proportional hazards model adjusted for known predictors (age, NYHA functional class, and glomerular filtration rate) of hospitalization in patients with heart failure. We assessed for a potential interaction between diabetes status and treatment group (sildenafil vs. placebo) with respect to change (from baseline to 24 weeks) in peak Vo_2 and 6-min walk distance, and the number of patients with ≥1 hospitalizations during the study period using linear or logistic regression as appropriate. A p value ≤0.05 was considered significant for all analyses. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

CLINICAL CHARACTERISTICS. Of the 216 patients with HFpEF enrolled in the RELAX study, there were 93 (43%) with diabetes. Compared with nondiabetic patients, diabetic patients were younger, more obese, and more often male and had a higher prevalence of comorbidities, including hypertension, ischemic heart disease, peripheral vascular disease, and obstructive lung disease (Table 1). Anemia tended to be more common in diabetic patients, and renal function was more impaired in diabetic patients with higher creatinine and cystatin-C levels and lower estimated glomerular filtration rate. At study entry, heart failure signs and symptoms and heart failure-related quality of life were similar between the groups. Diabetic patients were more often taking calcium channel blockers, statins, and diuretics, but there was no difference in the use of beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Most patients with diabetes were taking insulin or oral agents for glycemic control.

BIOMARKER PROFILE. HFpEF patients with or without diabetes had similar increase in NT-proBNP, but diabetic patients had higher levels of endothelin-1, a potent endogenous vasoconstrictor (Table 2). With respect to profibrotic markers, diabetic patients had higher galectin-3 and CITP levels, but increases in amino-terminal propeptide of procollagen type III did not achieve statistical significance. Diabetic patients had higher levels of uric acid and C-reactive protein, suggesting greater oxidative stress and inflammation, as well as a trend toward higher levels of hs-cTnI, suggesting more ongoing myocardial necrosis.

VENTRICULAR AND VASCULAR REMODELING AND FUNCTION. By echocardiography, LV mass index tended to be higher in diabetic patients, but relative wall thickness was similar in diabetic and nondiabetic patients (Table 3). Unadjusted LV cavity dimensions were similar, but LV end-diastolic dimension was smaller in diabetic patients when indexed for body surface area (BSA). Systolic performance was similar in diabetic and nondiabetic patients. Most diastolic function parameters were similar in diabetic and nondiabetic patients, although diabetic patients tended to have higher E/e′, suggesting higher LV filling

TABLE 1 Baseline Characteristics of HFpEF Patients With and Without Diabetes

Demographic/Clinical Characteristics	Non-DM (n = 123)	DM (n = 93)	p Value
Age, yrs	71 (63, 79)	66 (62, 73)	0.003
Female	57.7	35.5	0.001
Self-reported white race	93.5	88.2	0.17
Body surface area, m^2	2.02 (1.86, 2.21)	2.23 (2.06, 2.47)	<0.001
Body mass index, kg/m^2	30.7 (27.6, 34.2)	37.1 (32.3, 42.0)	<0.001
Heart rate, beats/min	68 (61, 78)	70 (62, 78)	0.74
Systolic blood pressure, mm Hg	126 (113, 138)	128 (114, 137)	0.97
Comorbidities			
Ischemic heart disease	33	47	0.03
Hypertension	77	95	<0.001
Peripheral vascular disease	7	25	<0.001
Obstructive lung disease	12	29	0.002
Hyperlipidemia	70	80	0.11
Atrial fibrillation or flutter	55	46	0.19
Anemia*	30	42	0.06
Hemoglobin, g/dl	13.0 (12.1, 14.0)	12.8 (11.7, 13.7)	0.10
Blood urea nitrogen, mg/dl	22 (16, 25)	28 (20, 39)	0.001
Creatinine	1.05 (0.83, 1.29)	1.21 (0.89, 1.70)	<0.001
Glomerular filtration rate, ml/min/1.73 m^2	67.5 (51.1, 83.6)	57.1 (39.2, 78.9)	0.02
Cystatin C	1.19 (1.03, 1.55)	1.59 (1.14, 1.97)	<0.001
Heart failure			
Jugular venous pressure ≥8 cm	47	44	0.68
Edema	16	26	0.09
NYHA functional class			0.34
II	50	43	
III	50	57	
MLHFQ total score	42 (30, 58)	47 (26, 68)	0.20
Medications at enrollment			
Beta-blocker	76	76	0.90
ACE-I or ARB	67	75	0.17
Aldosterone antagonist	11	11	0.97
Calcium channel blocker	24	40	0.01
Statin	54	76	<0.001
Loop diuretic	72	83	0.07
Any diuretic	82	91	0.046
Diabetes therapy			
Insulin treated	–	42	–
Oral medications alone	–	47	–
Diet alone	–	11	–

Values are median (25th, 75th percentiles) or %. *Hemoglobin <13 g/dl for men, <12 g/dl for women.
ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DM = diabetes mellitus; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NYHA = New York Heart Association.

TABLE 2 Biomarker Profile of HFpEF Patients With and Without Diabetes

Biomarkers (Core Laboratory)	Non-DM (n = 123)	DM (n = 93)	p Value
NT-proBNP	713 (303, 1593)	648 (280, 1553)	0.73
cGMP	77 (58, 102)	79 (56, 101)	0.99
Endothelin-1	2.3 (1.8, 3.0)	2.5 (2.0, 3.5)	0.05
Aldosterone	182 (122, 286)	202 (117, 274)	0.97
PIIINP	7.5 (6.1, 8.9)	8.2 (6.0, 10.9)	0.11
Galectin-3	13.1 (10.6, 16.0)	15.5 (12.2, 21.4)	<0.001
CITP	5.7 (4.5, 7.5)	7.8 (5.5, 12.4)	<0.001
Uric acid	6.8 (5.5, 8.5)	7.8 (6.3, 9.4)	0.005
C-reactive protein	3.3 (1.6, 7.3)	4.5 (2.1, 10.0)	0.015
hs-cTnI	8.3 (4.7, 16.5)	10.6 (6.5, 20.9)	0.10

Values are median (25th, 75th percentiles).
CITP = carboxy-terminal telopeptide of collagen type I; cGMP = cyclic guanosine monophosphate; DM = diabetes mellitus; hs-cTnI = high sensitivity cardiac troponin I; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PIIINP = amino-terminal propeptide of procollagen type III.

pressures. Although unadjusted left atrial volumes were similar, left atrial volume indexed to BSA was smaller in diabetic patients. Echocardiographic measurements of pulmonary and systemic vascular function were similar in diabetic and nondiabetic patients.

In the subgroup of patients who underwent CMR (n = 117), indexed LV mass was higher in diabetic than nondiabetic patients, whereas LV volumes (indexed to BSA) were similar. Aortic stiffness and systemic vascular resistance were similar in diabetic and nondiabetic patients.

EXERCISE CAPACITY. Compared with nondiabetic patients, diabetic patients had a lower peak Vo_2 (absolute and percentage predicted) (**Fig. 1**, Online Table 1), despite similar effort (similar respiratory exchange ratio). Submaximal exercise performance also was impaired in diabetic patients as evidenced by lower Vo_2 at the ventilatory anaerobic threshold and absolute and percentage predicted 6-min walk distance ($p < 0.05$ for all) (**Fig.1** and Online Table 1). Among diabetic patients, there was a trend toward a lower peak Vo_2 in those treated with versus without insulin (10.9 [9.4, 12.9] vs. 11.6 [10.1, 13.8] ml/kg/min, $p = 0.07$). The chronotropic index was lower, and the prevalence of chronotropic incompetence was higher in diabetic than nondiabetic patients, whereas peak systolic blood pressure was similar between groups. After adjusting for age, sex, and exercise modality, diabetes was associated with a 2.09 ml/kg/min lower peak Vo_2 ($p < 0.001$) (Online Table 2). After additional sequential adjustment for factors (body mass index, hemoglobin, and chronotropic index) that are known to influence peak exercise performance and potential mechanisms for the adverse effect of diabetes on exercise performance, the relationship between diabetes and a lower peak Vo_2 was attenuated but remained significant (Online Table 2). Similar findings were observed in multivariable analyses evaluating the relationship between diabetes and 6-min walk distance (Online Table 2).

CLINICAL OUTCOMES. Compared with nondiabetic patients, at study enrollment, diabetic patients had more frequently been hospitalized at least once for heart failure over the preceding 12 months (47% vs. 28%, $p = 0.004$) (**Fig. 2A**). During the 6-month study period, diabetic patients were more likely to be

TABLE 3 Ventricular and Vascular Remodeling and Function in HFpEF Patients With and Without Diabetes

	Non-DM (n = 123)		DM (n = 93)		
Echocardiographic Data	**n**	**Median (25th, 75th)**	**n**	**Median (25th, 75th)**	**p Value**
LV structure					
LV mass, g/ht$^{1.7}$	92	63 (50, 81)	66	69 (57, 88)	0.12
LV end-diastolic dimension, cm	98	4.6 (4.2, 5.1)	66	4.6 (4.3, 5.2)	0.46
LV end-diastolic dimension/BSA, cm/m^2	98	2.3 (2.1, 2.5)	66	2.1 (1.9, 2.3)	0.001
Relative wall thickness	92	0.40 (0.35, 0.45)	66	0.41 (0.38, 0.50)	0.11
LV systolic function					
EF, %	123	60 (56, 65)	90	60 (55, 65)	0.47
Stress corrected mFS	78	14.2 (12.5, 16.3)	58	14.7 (12.7, 16.5)	0.50
Cardiac index, l/min/m^2	102	2.5 (2.1, 2.8)	73	2.4 (2.0, 2.9)	0.78
LV diastolic function					
Medial e′	113	0.06 (0.04, 0.08)	84	0.06 (0.05, 0.08)	0.64
Lateral e′	113	0.08 (0.06, 0.10)	79	0.09 (0.06, 0.11)	0.91
E/e′ (medial)	108	14.6 (11, 22)	80	18.0 (13, 25)	0.054
E/A ratio	78	1.5 (1.0, 2.3)	64	1.4 (1.0, 2.0)	0.70
Deceleration time, ms	110	185 (152, 216)	83	187 (157, 233)	0.32
LA volume, ml	90	94 (75, 121)	59	89 (70, 112)	0.34
LA volume index, ml/m^2	90	47 (39, 60)	59	41 (32, 55)	0.02
Systemic and pulmonary artery function					
Pulse pressure, mm Hg	118	55 (47, 68)	89	58 (48, 69)	0.32
Arterial elastance, mm Hg/ml	103	1.6 (1.3, 1.9)	75	1.4 (1.2, 1.9)	0.10
SVR, dyne/s/cm^{-5}	102	1,453 (1,150, 1,699)	73	1,322 (1,085, 1,638)	0.16
SAC, ml/mm Hg	103	1.3 (1.1, 1.7)	75	1.5 (1.1, 1.9)	0.17
PA systolic pressure, mm Hg	87	41 (34, 49)	51	43 (32, 54)	0.87
CMR data					
EF, %	69	66 (60, 72)	48	65 (54, 69)	0.10
Cardiac index, l/min/m^2	69	2.3 (1.9, 2.7)	46	2.4 (2.0, 2.8)	0.87
LV mass, g/ht$^{1.7}$	69	50 (43, 58)	48	65 (53, 76)	<0.001
LV end-diastolic volume, ml	69	110 (91, 133)	48	128 (104, 156)	0.002
LV end-diastolic volume/BSA, ml/m^2	69	55 (48, 66)	48	58 (46, 69)	0.44
Aortic elastance, mm Hg/ml	69	1.6 (1.4, 1.9)	44	1.5 (1.1, 1.8)	0.17
Aortic distensibility, 10^{-3} mm Hg	54	1.1 (0.6, 1.5)	32	1.5 (0.9, 2.3)	0.051
SVR, dyne/s/cm^{-5}	69	1,488 (1,274, 1,880)	44	1,388 (1,132, 1,698)	0.10

BSA = body surface area; CMR = cardiac magnetic resonance; DM = diabetes mellitus; EF = ejection fraction; LA = left atrial; LV = left ventricular; mFS = midwall fractional shortening; PA = pulmonary artery; SAC = systemic arterial compliance; SVR = systemic vascular resistance.

hospitalized (≥1 time) for cardiac or renal causes than nondiabetic patients (23.7% vs. 4.9%, p < 0.001) (Fig. 2B). After adjustment for age, NYHA functional class, and glomerular filtration rate, diabetes remained a significant predictor of hospitalization for cardiac or renal causes during the 6-month study period (hazard ratio: 4.08, 95% confidence interval: 1.60 to 10.36, p = 0.003).

RESPONSE TO SILDENAFIL. There was no interaction between diabetes status and treatment group (sildenafil vs. placebo) with respect to the RELAX primary endpoint of change in peak Vo_2 (interaction p = 0.49) from baseline to 24 weeks or change in 6-min walk distance (interaction p = 0.30). There was also no interaction between diabetes status and treatment group with respect to hospitalizations for cardiac or renal causes during the study period (interaction p = 0.80).

DISCUSSION

We found that in a cohort of patients with objective evidence of HFpEF and reduced exercise capacity, diabetic patients had a more severe disease phenotype characterized by more numerous comorbidities, increased left ventricular hypertrophy, and increased circulating markers of vasoconstriction, oxidative stress, inflammation, and fibrosis. Adjusting for known determinants of peak exercise capacity, diabetic patients had a significantly lower peak Vo_2 and 6-min walk distance. Patients with diabetes had more hospitalizations both before and

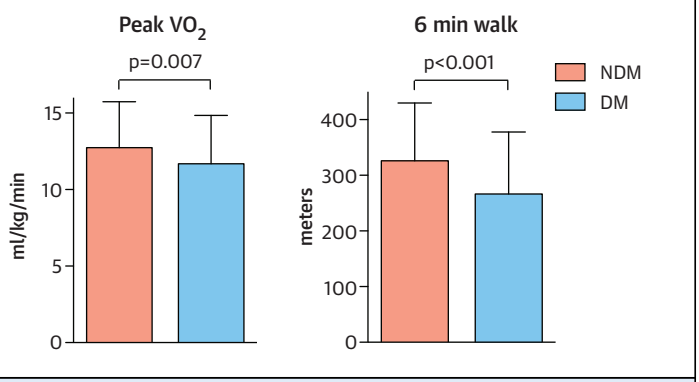

FIGURE 1 Exercise Capacity in HFpEF Patients With and Without Diabetes

Data shown as mean and SD. DM = diabetes mellitus; HFpEF = heart failure with preserved ejection fraction; NDM = no diabetes mellitus; VO_2 = volume of oxygen utilization.

after study entry. These findings are consistent with a recent novel HFpEF paradigm described by Paulus and Tschöpe (18) and underscore that diabetic HFpEF patients are at particularly high risk given their comorbidity burden and somewhat distinctive pathophysiology. These data are relevant to the design and interpretation of clinical trials enrolling HFpEF patients and support the need for therapeutic strategies targeting the pathophysiology of diabetic HFpEF patients.

Analyses from several other studies compared diabetic with nondiabetic patients with HFpEF and report worse outcomes in diabetic patients, including increased mortality and hospitalizations (3,4,13). Among patients with preserved EF (>40%) in CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), diabetes was associated with a 2-fold increase in cardiovascular death or hospitalization for heart failure after multivariable adjustment and an 80% increase in the hazard of all-cause mortality (3). In a secondary analysis of the Digitalis Investigation Group study, diabetic patients with EF >45% had an adjusted hazard ratio of 1.68 for heart failure death or hospitalization (4). We confirm the adverse prognostic impact of diabetes in HFpEF and extend these previous studies in several ways. The RELAX trial differed from other comparable studies in that it was restricted to patients with an EF >50% and had rigorous entry criteria to select patients with documented cardiac limitation to exercise and increased filling pressures by biomarker, invasive, or echocardiographic criteria (7,8). The RELAX trial also included a formal, detailed assessment of exercise capacity, distinguishing it from these previous studies. Finally, diabetes was also more common in the RELAX cohort (43%) than other comparable studies (17% to 32%), a fact that may reflect the entry criteria for the RELAX study, which resulted in a cohort with more advanced HFpEF (5–7,19).

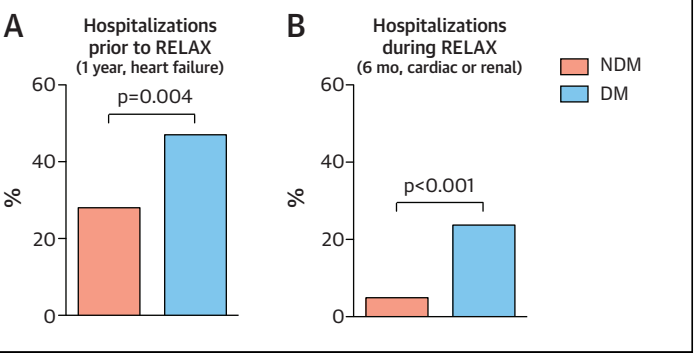

FIGURE 2 Hospitalizations in HFpEF Patients With and Without diabetes

Data are shown for HFpEF patients with and without diabetes for the prevalence of at least 1 heart failure hospitalization during the 12-month period before enrollment in RELAX **(A)** and for the percentage of patients with ≥1 hospitalization for cardiac or renal causes during the 6-month trial period **(B)**. Abbreviations as in Figure 1.

BIOMARKER PROFILE IN HFpEF PATIENTS WITH DIABETES. Previous studies comparing diabetic and nondiabetic patients with HFpEF have not included a detailed biomarker profile. Using a panel of biomarkers that evaluated multiple biological pathways, we found that diabetic HFpEF patients have increased mediators of vasoconstriction (endothelin-1) and fibrosis (CITP, galectin-3), increased oxidative stress (uric acid), and inflammation (C-reactive protein) and a suggestion of greater ongoing myocardial necrosis (hs-cTnI). Diabetes is characterized by a complex milieu of hyperinsulinemia, insulin resistance, hyperglycemia, and increased circulating and intramyocardial nonesterified fatty acids (20); these biomarker data provide insight into the ways in which diabetes may exacerbate and intensify the pathophysiology of HFpEF, which adversely affects clinical outcomes. Despite a modestly higher LV filling pressure in diabetic patients as evidenced by a higher E/e′, there was no difference in NT-proBNP levels, which may have been due to a greater prevalence of obesity in the diabetic patients.

VENTRICULAR AND VASCULAR STRUCTURE AND FUNCTION IN DIABETIC PATIENTS WITH HFpEF. Of the previous studies that compared diabetic and nondiabetic patients with HFpEF (3,4,13), only 1 provided a detailed comparison of ventricular and

vascular structure and function (13). Consistent with Mohammed et al. (13), we observed that systolic function is similar between diabetic and nondiabetic patients; indices of LV relaxation and stiffness were also similar, whereas LV filling pressures (E/e′) tended to be higher in diabetic patients. We also observed increased LV hypertrophy in diabetic patients. Surprisingly, left atrial volume and LV end-diastolic dimension indexed to BSA were lower in diabetic patients, which may reflect "overcorrection" by indexing to BSA in obese patients. Resting measures of vascular function, including pulsatile and resistive load, were similar between diabetic and nondiabetic patients.

EXERCISE CAPACITY IN DIABETIC PATIENTS WITH HFpEF. Diabetic patients had worse maximal and submaximal exercise performance, which had not been previously evaluated in patients with HFpEF. Although we cannot determine the causative mechanisms for the worse exercise performance exhibited by diabetic patients due to the correlative study design used, our data do provide important insights to be further examined in future studies. We observed significant differences in exercise capacity despite a lack of difference in resting systolic or diastolic cardiac function (except for a trend for E/e′) or systemic or peripheral vascular pressures or function. In contrast, despite a similar resting HR and similar prevalence of beta-blocker use, there was a marked difference in the chronotropic index between diabetic and nondiabetic patients. Recent studies demonstrated the important contribution of peripheral, noncardiac factors to exercise performance (21,22). An increase in HR is a critical part of increasing cardiac output and has been shown to be an important contributor to exercise capacity (21–23). Cardiovascular autonomic neuropathy is a known complication of diabetes, which includes diminished exercise capacity due to impaired parasympathetic and sympathetic responses that would normally increase cardiac output and blood flow to exercising muscles (24). The withdrawal and reactivation of vagal tone are thought to be important underlying mechanisms for HR changes during exercise (25). HFpEF patients have a slower HR increase, lower peak HR, and impaired recovery (22). An attenuated HR response to exercise is associated with increased mortality as is slower heart recovery after exercise, which was more common in diabetic patients (25,26).

Beyond differences in HR, there may be differences in peripheral oxygen use that may explain, in part, the reduced exercise capacity in diabetic compared with nondiabetic patients with HFpEF. A significant contributor to reduced peak V_{O_2} in patients with HFpEF is reduced arteriovenous oxygen content difference, which is due to reduced O_2 delivery or reduced O_2 extraction in exercising muscles (21,27). Decreased O_2 delivery may occur in diabetic patients with HFpEF due to a greater prevalence of anemia (a trend was seen in our data) or less vasodilator reserve due to autonomic dysfunction, an increased prevalence of peripheral vascular disease, or impaired endothelial function from oxidative stress, inflammation, and vasoconstriction (consistent with the biomarker increases we observed in diabetic patients with HFpEF). Abnormalities in oxygen delivery and extraction have been observed in diabetic patients (28,29).

Additionally, older and emerging studies demonstrate that differences in skeletal muscle function, composition, and strength explain important differences in exercise capacity in heart failure patients with reduced and preserved EF (30–32). Although not examined in this study, diabetes has been shown to affect skeletal muscle composition and function likely due to multiple factors including inflammation, obesity, insulin resistance, fatty acid oxidation, oxidative stress, and impaired mitochondrial function (33–35). Obesity also impairs exercise capacity and often coexists with diabetes. Although there is likely some overlap in the mechanisms by which diabetes and obesity adversely affect exercise capacity, we found that diabetes was still associated with reduced exercise performance, even after controlling for a large difference in BMI. Other studies demonstrated that diabetes, particularly the degree of insulin resistance, has a greater adverse effect on exercise capacity than obesity (35,36).

Collectively, these data suggest that the reduced exercise capacity of diabetic patients with HFpEF is largely due to peripheral factors, including impaired chronotropic reserve, reduced peripheral oxygen use, and altered skeletal muscle function. Further studies are needed to carefully examine these mechanisms, as well as to evaluate the contractility and vasodilator reserve of diabetic patients with HFpEF. Given the more marked impairment in exercise capacity among diabetic patients with HFpEF, it seems even more important to encourage exercise training in these individuals, which has been shown to improve exercise capacity and quality of life in patients with HFpEF, largely through its effect on peripheral mechanisms (37,38).

STUDY LIMITATIONS. Our study has several limitations to consider when interpreting the results. The enrolling sites determined the diagnosis of diabetes,

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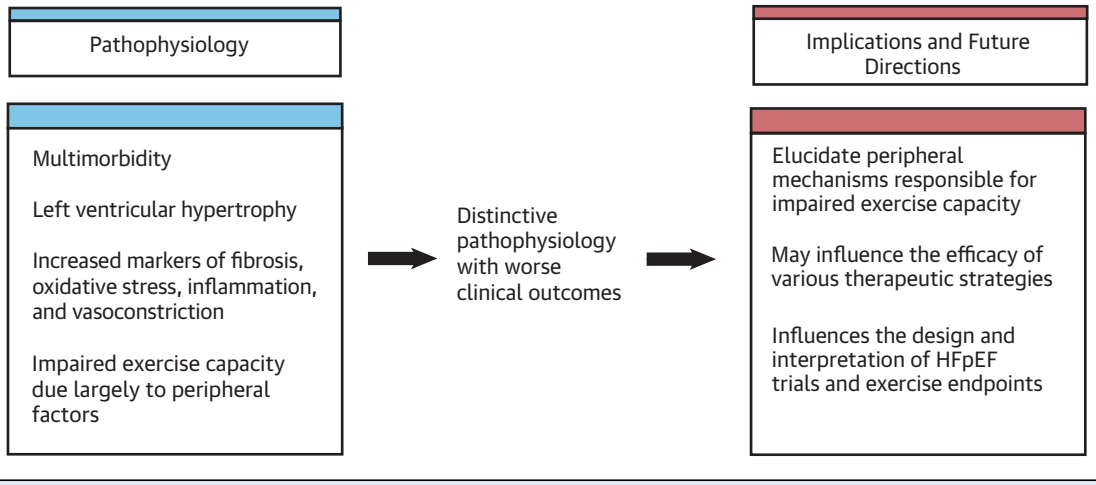

CENTRAL ILLUSTRATION **Diabetes and HFpEF: New Insights and Future Directions**

Distinctive pathophysiology with worse clinical outcomes can influence future direction for these patients. HFpEF = heart failure with preserved ejection fraction.

and it was not verified by other mechanisms. We do not have access to data on the severity or duration of diabetes, microvascular complications, or glucose control. Although the detailed phenotyping of patients was a strength of the study, the relatively small number of patients included may prevent us from detecting significant, smaller magnitude, differences between the diabetic and nondiabetic patients. Further, the small number of patients and clinical events limits the power of our interaction analyses and our ability to adjust for confounders in the Cox model for hospitalization. Finally, we do not have detailed hemodynamic and echocardiographic data at peak exercise that would provide insight into the effect of diabetes on cardiac and vascular reserve function.

CONCLUSIONS

In a carefully phenotyped population of patients with HFpEF, those with diabetes were at increased risk of hospitalization. Multimorbidity, impaired chronotropic reserve, LV remodeling, and activation of inflammatory, pro-oxidative, vasoconstrictor, and profibrotic pathways may contribute to adverse outcomes in HFpEF patients with diabetes. The mechanisms of impaired exercise performance in diabetic patients are multifactorial, but appear to be largely due to peripheral factors. Our findings support the need for therapeutic strategies targeting the distinctive pathophysiology of diabetes in HFpEF (**Central Illustration**) and have implications for the design of clinical trials evaluating the HFpEF population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Among patients with heart failure who have preserved left ventricular ejection fraction, those with diabetes have a more severe disease phenotype, more extensive comorbidities, greater left ventricular hypertrophy, and higher circulating markers of vasoconstriction, oxidative stress, inflammation, and fibrosis.

COMPETENCY IN MEDICAL KNOWLEDGE 2: More severely impaired exercise tolerance in diabetic patients with heart failure and preserved left ventricular ejection fraction is due mainly to extracardiac factors.

TRANSLATIONAL OUTLOOK: Future studies should be directed toward understanding the distinctive pathophysiology and extracardiac mechanisms that contribute to reduced exercise capacity in diabetic patients who have heart failure with preserved left ventricular ejection fraction and addressing these in the design of clinical trials.

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KEY WORDS biomarkers, diabetes mellitus, exercise capacity, heart failure with preserved ejection fraction, left ventricular structure

APPENDIX For supplemental tables, please see the online version of this article.